

5 WHAT IS CLAIMED IS:

1. A method for detecting one or more non-nucleic acid analytes, the method comprising:

10 (a) providing at least one fusion polypeptide with specificity for a non-nucleic acid analyte, which polypeptide comprises a first inactive functional domain; an analyte binding domain; and a second inactive functional domain;

wherein binding of the analyte results in a conformational change which brings the first inactive functional domain and the second inactive functional domain into proximity, thereby converting the first and second inactive functional domains into an optically detectable functional domain,

15 (b) contacting the fusion polypeptide with a sample comprising the analyte; and,

(c) detecting the conformational change induced by binding of the non-nucleic acid analyte, wherein the non-nucleic acid analyte is selected from the group consisting of a small organic molecule, a peptide, a polypeptide and a dissolved gas.

20 2. The method of claim 1, wherein the first and second inactive functional domains are derived from a green fluorescent protein or a green fluorescent protein homologue.

3. The method of claim 1, comprising detecting an electrochemical signal produced by binding of the analyte.

25 4. The method of claim 1, comprising detecting an optical signal produced by binding of the analyte.

30 5. The method of claim 4, wherein the optical signal is detected by one or more of: ultraviolet spectrophotometry, visible light spectrophotometry, surface plasmon resonance; calorimetry, fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD).

- 5 **6.** The method of claim 4, wherein the optical signal is produced by displacement of a tethered substrate upon binding of the analyte.
- 7.** The method of claim 6, wherein the tethered substrate is an analyte analogue.
- 8.** The method of claim 1, comprising providing a physical or logical
10 array comprising a plurality of polypeptides.
- 9.** The method of claim 8, wherein the plurality of polypeptides comprise a plurality of different analyte binding specificities.
- 10.** The method of claim 10, wherein the plurality of polypeptides provide a common signal.
- 15 **11.** The method of claim 1, wherein the analyte comprises a hormone or a metabolite.
- 12.** The method of claim 1, wherein the sample is a biological sample or an environmental sample.
- 13.** The method of claim 12, wherein the biological sample is selected
20 from the group consisting of blood, plasma, urine, sweat, cerebrospinal fluid and tears.
- 14.** A method for detecting one or more non-nucleic acid analytes, the method comprising:
- (a) providing at least one fusion polypeptide with specificity for a non-nucleic acid analyte, which polypeptide comprises a first inactive functional domain; an
25 analyte binding domain; and a second inactive functional domain;
- wherein binding of the analyte results in a conformational change which brings the first inactive functional domain and the second inactive functional domain into proximity, thereby converting the first and second inactive functional domains into a catalytic functional domain;
- 30 (b) providing a substrate for the catalytic functional domain;
- (c) contacting the fusion polypeptide with a sample comprising the analyte; and,

5 (d) detecting the conversion of the substrate to a product.

15. The method of claim 14, wherein conversion of the substrate to a product is detected by detecting an electrochemical signal.

16. The method of claim 14, wherein conversion of the substrate to a product is detected by detecting an optical signal.

10 17. The method of claim 14, wherein the optical signal is detected by one or more of: ultraviolet spectrophotometry, visible light spectrophotometry, surface plasmon resonance; fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD).

15 18. The method of claim 14, comprising providing a physical or logical array comprising a plurality of polypeptides.

19. The method of claim 18, wherein the plurality of polypeptides comprise a plurality of different analyte binding specificities.

20 20. The method of claim 19, wherein the plurality of polypeptides provide a common signal.

21. The method of claim 14, wherein the analyte comprises a small molecule.

22. The method of claim 14, wherein the small molecule comprises a hormone or a metabolite.

25 23. The method of claim 14, wherein the sample is a biological sample or an environmental sample.

24. The method of claim 23, wherein the biological sample is selected from the group consisting of blood, plasma, urine, sweat, cerebrospinal fluid and tears.

30 25. A method for detecting one or more non-nucleic acid analytes, the method comprising

5 (a) providing at least one polypeptide with specificity for a non-nucleic acid analyte, which polypeptide comprises an analyte binding domain and a catalytic domain, wherein binding of the analyte results in an allosteric conformational change which activates the catalytic domain resulting in conversion of a substrate to a detectable product; and,

10 (b) providing a substrate for the catalytic domain;
(c) contacting the polypeptide with a sample comprising the analyte; and,
(d) detecting the product produced by activity of the catalytic domain on the substrate.

15 **26.** The method of claim 25, wherein conversion of the substrate to product produces an electrochemical signal.

27. The method of claim 25, wherein conversion of the substrate to product produces an optical signal.

20 **28.** The method of claim 27, wherein the optical signal is detected by one or more of: a charge coupled device, ultraviolet spectrophotometry, visible light spectrophotometry, fluorimetry, colorimetry, surface plasmon resonance; fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD).

25 **29.** The method of claim 25, comprising providing a physical or logical array comprising a plurality of polypeptides.

30. The method of claim 29, wherein the plurality of polypeptides comprise a plurality of different analyte binding specificities.

31. The method of claim 30, wherein conversion of substrate to product by the analyte-bound plurality of polypeptides is detected by detecting a common signal.

30 **32.** The method of claim 25, wherein the sample is a biological sample, an environmental sample, or an industrial sample.

- 5 **33.** The method of claim 32, wherein the biological sample is selected from the group consisting of blood, plasma, urine, sweat, cerebrospinal fluid and tears.
- 34.** The method of claim 25, wherein the analyte comprises a small molecule.
- 35.** The method of claim 25, wherein the analyte comprises a hormone, a
10 metabolite or an ion.
- 36.** The method of claim 25, wherein the analyte comprises an antigen or a ligand.
- 37.** The method of claim 25, wherein the sample further comprises an agonist or an antagonist.
- 15 **38.** A method for detecting an analyte, the method comprising:
 (a) providing at least one biopolymer, which biopolymer undergoes a conformational change upon binding to an analyte;
 (b) contacting a sample comprising the analyte to the biopolymer; and,
 (c) detecting the conformation change induced by binding of the analyte,
20 wherein the analyte is not an ion.
- 39.** The method of claim 38, comprising contacting a biological sample or an environmental sample.
- 40.** The method of claim 39, wherein the biological sample comprises blood, plasma, urine, sweat, cerebrospinal fluid, or tears.
- 25 **41.** The method of claim 38, wherein the at least one biopolymer comprises a polypeptide.
- 42.** The method of claim 41, wherein the polypeptide comprises an antibody or a receptor.
- 43.** The method of claim 38, wherein the conformation change results in
30 generation of an optical signal.

5 **44.** The method of claim 43, wherein the optical signal is detected by one or more of: surface plasmon resonance; fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD).

10 **45.** The method of claim 43, wherein the optical signal is produced by displacement of a tethered substrate upon binding of the analyte.

46. The method of claim 45, wherein the tethered substrate is an analyte analogue.

15 **47.** The method of claim 38, comprising providing a physical or logical array comprising a plurality of polypeptides.

48. The method of claim 47, wherein the plurality of polypeptides comprise a plurality of different analyte binding specificities.

49. The method of claim 48, wherein the plurality of polypeptides provide a common signal.

20 **50.** The method of claim 38, wherein the analyte comprises a small molecule.

51. The method of claim 38, wherein the analyte comprises a hormone or a metabolite.

52. A method for identifying a physiologic state, the method comprising:
25 (a) providing at least one biopolymer, which biopolymer undergoes a conformational change upon binding to a marker associated with a physiologic state;
 (b) contacting the biopolymer with a biological sample comprising the marker, and,
 (c) detecting the conformation change induced by binding of the marker,
30 thereby identifying the physiologic state associated with the marker.

5 **53.** The method of claim 53, wherein the sample comprises a biological sample selected from among: blood, plasma, urine, sweat, cerebrospinal fluid, or tears.

54. The method of claim 53, wherein the at least one biopolymer comprises a polypeptide.

10 **55.** The method of claim 54, wherein the polypeptide comprises an enzyme, an antibody, a receptor or a fusion protein.

56. The method of claim 54, wherein the polypeptide comprises a fusion protein having a first inactive functional domain; an analyte binding domain; and a second inactive functional domain.

15 **57.** The method of claim 56, wherein binding of the analyte results in a conformational change which brings the first inactive functional domain and the second inactive functional domain into proximity, thereby converting the first and second inactive functional domains into a functional catalytic or fluorescent domain.

58. The method of claim 57, wherein the conformation change results in generation of an optical signal.

20 **59.** The method of claim 52, wherein the optical signal is detected by one or more of: ultraviolet spectrophotometry, visible light spectrophotometry, surface plasmon resonance; fluorescence polarization; fluorescence quenching; colorimetric quenching; fluorescence wavelength shift; fluorescence resonance energy transfer (FRET); enzyme linked immunosorbent assay (ELISA) or liquid crystal displays (LCD).

25 **60.** The method of claim 52, wherein the optical signal is produced by displacement of a tethered substrate upon binding of the analyte.

61. The method of claim 60, wherein the tethered substrate is an analyte analogue.

30 **62.** The method of claim 52, comprising providing a physical or logical array comprising a plurality of polypeptides.

5 **63.** The method of claim 62, wherein the plurality of polypeptides
comprise a plurality of different analyte binding specificities.

64. The method of claim 63, wherein the plurality of polypeptides provide
a common signal.

10 **65.** The method of claim 52, wherein the analyte comprises a small
molecule.

66. The method of claim 52, wherein the analyte comprises a hormone or
a metabolite.

67. A biosensor comprising:

(a) a support; and,

15 (b) at least one polypeptide with specificity for a non-nucleic acid analyte,
which polypeptide comprises an analyte binding domain and a catalytic domain, wherein
binding of the analyte results in an allosteric conformational change which activates the
catalytic domain resulting in conversion of a substrate to a detectable product; which at
least one polypeptide is immobilized on the support.

20 **68.** A biosensor comprising:

(a) a support; and,

25 (b) at least one fusion polypeptide with specificity for a non-nucleic acid
analyte, which polypeptide comprises a first inactive functional domain; and analyte
binding domain; and a second inactive functional domain; wherein binding of the analyte
brings the first inactive functional domain and the second inactive functional domain into
proximity, thereby converting the first and second inactive functional domains into a
functional catalytic or optically detectable domain; which at least one fusion polypeptide
is immobilized on the support.

30 **69.** A biosensor comprising:

(a) a solid support;

(b) a plurality of polypeptides immobilized on the solid support, wherein
the plurality comprises polypeptides having different analyte binding specificities; and,

(c) a detection system.

5 **70.** The biosensor of claim 69, further comprising a conductive element or an optically detectable element.

71. The biosensor of claim 69, wherein the plurality of polypeptides is immobilized with an immobilization matrix selected from the group consisting of carbon paste and a non-biological polymeric matrix.

10 **72.** The biosensor of claim 69, wherein the biosensor further comprises a display.

73. A method of sensing one or more test stimulus, the method comprising:

15 providing a library of biopolymers comprising nucleic acid variants or expression products of the nucleic acid variants;
 arraying the library in a spatial or logical format to provide a physical or logical array;

20 contacting one or more calibrating stimulus to the array, whereby one or more members of the array produce one or more detectable signals in response to contact by the one or more calibrating stimulus, thereby producing a calibrating array pattern which identifies contact of the array by the one or more calibrating stimulus;

 contacting at least one test stimulus to the array, thereby producing a test stimulus array pattern; and,

25 comparing the test stimulus array pattern to the calibrating array pattern, thereby identifying the test stimulus.

74. A method of using a re-usable array of biopolymers, the method comprising:

 providing a physical or logical array of biopolymers comprising nucleic acid variants or expression products of the nucleic acid variants;

30 contacting the physical or logical array with one or more first stimulus;

 observing a first resulting response of the array, or collecting a first product resulting from contact between the array and the first stimulus;

 reusing the array by contacting the array a second time with the first stimulus, or with a second stimulus; and,

5 observing a second resulting response of the array, or collecting a second product resulting from contact between the array and the first or second stimulus; and, optionally, comparing the first resulting response of the array to the second resulting response of the array.

10 **75.** The method of claim 73 or 74, wherein the biopolymer library comprises or is encoded by recursively recombined nucleic acids.

76. The method of claim 73 or 74, wherein the biopolymer library comprises or is encoded by artificially mutated or artificially shuffled nucleic acids.

77. The method of claim 73 or 74, wherein the biopolymer library comprises or is encoded by species variants of one or more nucleic acids.

15 **78.** The method of claim 73 or 74, wherein the biopolymer library comprises or is encoded by nucleic acids produced by recursive recombination of species variants of one or more nucleic acids.

79. The method of claim 73 or 74, wherein the biopolymer library comprises photoactivatable members.

20 **80.** The method of claim 79, the method comprising masking a portion of the array and exposing the resulting masked array to light.

81. The method of claim 73 or 74, wherein the array comprises one or more of: a conductive member, a capacitive member, an optically responsive member, an electrically responsive member, and an electrically or logically gated or gateable member.

82. The method of claim 73 or 74, wherein the array comprises one or more of: a bio-laser, a polychromic display, a molecular poster, a bar code, a protein TV, a molecular camera, a UV molecular camera, an IR molecular camera, or a flat screen display.

30 **83.** The method of claim 73 or 74, wherein the array members comprise one or more proteins.

5 **84.** The method of claim 83, wherein the proteins comprise electrically
conductive proteins.

85. The method of claim 83, wherein the proteins are purified.

86. The method of claim 83, wherein the proteins comprise one or more
purification tags.

10 **87.** The method of claim 86, wherein the purification tags are selected
from the group consisting of: His tags, and FLAG tags.

88. The method of claim 73 or 74, wherein arraying the biopolymer
library comprises arranging the members of the library in a logically accessible format.

15 **89.** The method of claim 73 or 74, wherein arraying the biopolymer
library comprises arranging the members of the library in a physically gridded format.

90. The method of claim 73 or 74, wherein arraying the biopolymer
library comprises plating the members of the library in microtiter trays.

20 **91.** The method of claim 73 or 74, wherein arraying the biopolymer
library or expression product library comprises recording the position of members of the
library in one or more database.

92. The method of claim 73 or 74, wherein arraying biopolymer library
comprises arranging the members of the library for parallel examination.

25 **93.** The method of claim 73 or 74, wherein arraying the biopolymer
library or expression product library comprises arranging the members of the library for
sequential examination.

94. The method of claim 73 or 74, wherein the first, second, test or
calibrating stimulus are simultaneously contacted to a plurality of biopolymer library
members.

5 **95.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are sequentially contacted to a plurality of biopolymer library members.

96. The method of claim 73 or 74, wherein a plurality of first, second, test or calibrating stimulus are contacted to a plurality of biopolymer members.

10 **97.** The method of claim 96, wherein contact of the plurality of first, second, test or calibrating stimulus produces a signature for a sample type.

98. The method of claim 97, wherein the signature is representative of one or more phenomenon selected from: a metabolic state of a cell, an operon induction in or by a cell, an induction of cell growth, a proliferation in or caused by a cell, a cancer of a cell or tissue, or organism, apoptosis, cell death, cell cycle, cell or tissue differentiation, tumorigenesis, disease state, drug resistance, drug efficacy, antibiotic spectrum, drug toxicity, gas level, SO_x, NO_x Alzheimers disease, infection, presence of viruses, viral infection, bacterial infection, HIV infection, AIDS, serum cholesterol, CHDL level, LDL, serum triglyceride level, blood glucose level, ion or gas production or
15 internalization, cytokine receptor expression, antibody-antigen interactions, pregnancy, fertility, fecundity, presence or absence of narcotics or other controlled substances, heart attack, presence or absence of steroids, body temperature, presence of sound waves, taste, scent, food composition, beverage composition, and an environmentally monitored condition.

25 **99.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are contacted to a plurality of library members in a microtiter plate.

100. The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are contacted to a plurality of library members fixed on a solid substrate.

30 **101.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are contacted to a plurality of library members, or expression products thereof, fixed on a solid substrate, wherein the solid substrate comprises a

5 Nickel-NTA coated surface, a silane-treated surface, a pegylated surface, or a treated surface.

102. The method of claim 73 or 74, wherein the biopolymer library members or expression products thereof are fixed to an organizational matrix in spatially addressable locations.

10 **103.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are contacted to a plurality of biopolymer library members, wherein member types are fixed on the surface of one or more beads.

104. The method of claim 103, wherein the one or more beads each comprise more than one detectable feature.

15 **105.** The method of claim 104, wherein the more than one detectable feature includes a first feature which identifies binding by the first, second, test or calibrating stimulus and a second feature which identifies either the type of bead or the type of library member or expression product thereof which is bound to the bead.

20 **106.** The method of claim 73 or 74, wherein the first stimulus, the second stimulus, the calibrating stimulus or the test stimulus, is selected from the group consisting of: light, radiation, an atom, an ion, and a molecule.

25 **107.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus comprises, hybridizes to, binds, acts upon or is acted upon by one or more of: radiation, a polymer, a chemical moiety, a biopolymer, a nucleic acid, an RNA, a DNA, a protein, a ligand, an enzyme, a chemo-specific enzyme, a regio-specific enzyme, a stereo-specific enzyme, a nuclease, a restriction enzyme, an restriction enzyme which recognizes a triplet repeat, a restriction enzyme that recognizes DNA superstructure, a restriction enzyme with an 8 base recognition sequence, an enzyme substrate, a regio-specific enzyme substrate, a stereo-specific enzyme substrate, a ligase,
30 a thermostable ligase, a polymerase, a thermostable polymerase, a co-factor, a lipase, a protease, a glycosidase, a toxin, a contaminant, a metal, a heavy metal, an immunogen, an antibody, a disease marker, a cell, a tumor cell, a tissue-type, cerebro-spinal fluid, a cytokine, a receptor, a chemical agent, a biological agent, a fragrance, a pheromone, a

5 hormone, an olfactory protein, a metabolite, a molecular camera protein, a rod protein, a cone protein, a light-sensitive protein, a lipid, a pegylated material, an adhesion amplifier, a drug, a potential drug, a lead compound, a protein allele, an oxidase, a reductase, or a catalyst.

10 **108.** The method of claim 73 or 74, wherein the first, second, test or calibrating stimulus are contacted to the members of the library by incubating a solution comprising the test molecule or the calibrating molecule with the library members.

109. The method of claim 108, wherein the solution is a fluid, a polymer solution or a gel.

15 **110.** The method of claim 73 or 74, wherein comparison of the test array pattern and the calibrating array pattern, or of the first resulting response of the array and the second resulting response of the array, is performed by a computer.

111. The method of claim 73 or 74, wherein a plurality of first, second, test or calibrating stimuli are contacted to the array to produce a plurality of resulting array patterns.

20 **112.** The method of claim 111, further comprising recording the plurality of resulting array patterns in one or more databases.

113. The method of claim 112, further comprising assigning a bar code to each resulting array pattern.

25 **114.** The method of claim 73 or 74, wherein the test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array, comprises variations in the presence or absence of signal at different locations on or in the array.

30 **115.** The method of claim 73 or 74, wherein the test array pattern, the calibrating array pattern, the first resulting response of the array, or the second resulting response of the array comprises variations in the level of signal at different locations on the array.

5 **116.** The method of claim 73 or 74, wherein the test array pattern, the
calibrating array pattern, the first resulting response of the array, or the second resulting
response of the array comprises variations in the presence and intensity of signal at
different locations on the array.

10 **117.** The method of claim 73 or 74, wherein an intensity of the test array
pattern, the calibrating array pattern, the first resulting response of the array, or the
second resulting response of the array comprises is measured to quantify the first,
second, test or calibrating stimulus.

15 **118.** The method of claim 73 or 74, wherein the test array pattern, the
calibrating array pattern, the first resulting response of the array, or the second resulting
response of the array comprises one or more fluorophore emission, photon emission,
chemiluminescent emission, coupled luminescent/fluorescent emission or quenching, or
detection of one or more fluorophore emission.

20 **119.** The method of claim 73 or 74, wherein the test array pattern, the
calibrating array pattern, the first resulting response of the array, or the second resulting
response of the array comprises an electrochemically detectable signal, an
amperometrically detectable signal, a potentiometrically detectable signal, a signal
detectable as a change in pH, a signal based on specific ion levels, a signal based on
changes in conductivity, a piezoelectric signal, a change in resonance frequency, a signal
detectable as surface acoustic waves, or a signal detectable by quartz crystal
25 microbalances.

120. The method of claim 118, wherein the test array pattern, the
calibrating array pattern, the first resulting response of the array or the second resulting
response of the array comprises multiple wavelengths of light.

30 **121.** The method of claim 118, wherein the test array pattern, the
calibrating array pattern, the first resulting response of the array or the second resulting
response of the array is generated by detection of one or more of: light, H₂O₂, glucose
oxidase, NADP, NADPH⁺, NAD(P)H reductase, a change in reduction potential, a
change in protein conformation, a change in intrinsic fluorescence, fluorescence,

5 luminescence, FRET, absorption, surface plasmon resonance, antigen binding, antibody binding, enzyme activity, opening of an ion channel, or label binding.

122. The method of claim 73 or 74, wherein at least one member of the biopolymer library, or an expression product thereof, is selected, prior to the arraying step, for one or more of: enhanced stability, orientation of protein binding, improved
10 production, cost of manufacture, optimal activity of expressed members which comprise a tag, overexpression mutations, optimized protein folding, permanent enzyme secretion, improved operators, improved ribosome binding sites, avidity, selectivity, production of a detectable side product, and detection limit.

123. The method of claim 73 or 74, wherein the test array pattern, the
15 calibrating array pattern, the first resulting response of the array or the second resulting response of the array are detected by one or more of: a microscope, a CCD, a phototube, a photodiode, an LCD, a scintillation counter, film, or visual inspection.

124. The method of claim 73 or 74, wherein the test array pattern, the
20 calibrating array pattern, the first resulting response of the array or the second resulting response of the array are digitized and stored in one or more database in one or more computer.

125. The biopolymer array produced by the method of claim 73 or 74.

126. The biopolymer array of claim 125, wherein the array is stable for at least one year under pre-selected storage conditions.

25 127. A computer comprising a data set corresponding to the labeling biopolymer sensor array pattern or test biopolymer sensor array pattern of claim 73 or 74.

128. The method of claim 73 or 74, further comprising contacting at least
30 one additional stimulus to the array, and comparing a resulting additional test stimulus array pattern to the calibrating array pattern, thereby identifying the at least one additional stimulus, or observing an additional resulting response of the array, or collecting an additional product resulting from contact between the array and the

5 additional or a previous stimulus, and optionally comparing the additional resulting response to any one or more previous responses of the array.

129. The method of claim 128, comprising contacting the array with two or more additional stimuli.

130. The method of claim 129, comprising contacting 10 or more
10 additional stimuli to the array.